



Maraviroc (MVC) Intensification for Suboptimal CD4+ Response Despite Sustained Virologic Suppression: ACTG 5256

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Abstract

Background: Despite viral suppression, antiretroviral therapy (ART) does not restore CD4 counts in some patients. MVC use is associated with enhanced CD4 recovery in patients who initiate ART. We therefore studied the effect of ART intensification with MVC on CD4 counts in patients with suboptimal CD4 recovery.

Methods: Single-arm pilot trial in subjects with a CD4 count <250/ μ L, a calculated CD4 slope between -20 and +20 cells/ μ L/year and undetectable plasma HIV-1 RNA for the 48 weeks prior to entry. Subjects added MVC, a CCR5 antagonist, to their existing ART regimen for 24 weeks. The primary endpoint was the change in CD4 counts from the average of the 2 baseline counts to the average of the week 22 and 24 counts on MVC. Extensive immunophenotyping was also performed at baseline, week 22 and 24. With a planned sample size of 32, MVC intensification would be considered successful if a CD4 count increase of <20 cells/ μ L was excluded based on a one-sided Wilcoxon signed-rank test.

Results: 34 subjects were enrolled. The median age was 50; 10 (29%) were non-white; 2 (6%) were women; the median baseline CD4 count was 153/ μ L. The median duration of HIV-1 RNA suppression was 3 years prior to entry. Two subjects discontinued MVC for virologic failure and were excluded per protocol. A CD4 count increase of <20 cells/ μ L was not excluded for the primary endpoint (p=0.97). The median increase in CD4 count to week 22/24 was 12 cells/ μ L [90% CI 1, 22]. Only 2 subjects had a CD4 increase of \geq 50 cells/ μ L. The median baseline immune activation and apoptosis markers in the CD4⁺ and CD8⁺ subsets and the change to week 22/24 are shown below. The change in %CD38⁺ was not associated with CD4 gain.

	Baseline (CD4 ⁺ subset)	Change to week 22/24 [90% CI]	Baseline (CD8 ⁺ subset)	Change to week 22/24 [90% CI]
%CD38 ⁺	45%	-15% [-20, -9]	30%	-14% [-20, -9]
%HLA-DR ⁺ /CD38 ⁺	5.3%	-1.3% [-1.8, -0.3]	8.7%	-1.4% [-3, -0.3]
%Ki67 ⁺	2.9%	-1.0% [-1.5, -0.5]	0.9%	-0.1% [-0.3, 0.1]
%caspase3 ⁺	1.7%	-1.1% [-1.4, -0.6]	1.1%	-0.7% [-0.9, -0.4]
%Bcl-2	1.7%	0.7% [0, 1.3]	1.3%	0.5% [-0.1, 0.8]

Conclusions: Adding MVC to a suppressive antiretroviral regimen was not associated with the hypothesized increase in CD4 counts. MVC intensification was associated with decreased immune activation as evidenced by reduced %CD38⁺, %HLA-DR⁺/CD38⁺, and improvement in markers of apoptosis. The clinical significance of these findings is unknown. Further studies of CCR5 antagonists to dampen immune activation associated with HIV infection are warranted.

Background

Low CD4+ T-cell counts despite ART

- A subgroup of patients have poor CD4 cell count reconstitution despite successful virologic suppression with ART
- Those with lower CD4+ T-cell counts remain at elevated risk for death, liver disease, non-AIDS defining cancers and other serious medical issues
- No successful strategies to restore CD4+ T-cell function
 - IL-2 causes CD4+ T-cell count increases but did not translate to clinical benefit

CCR5 antagonists and CD4+ T-cell gain

- Meta-regression of recent ART trials showed an added CD4 cell count increase of approximately 30 cells/ μ L with use of CCR5 antagonists compared to non-use controlling for virologic suppression
- Postulated mechanisms
 - CD4+ T-cell redistribution
 - Dampening immune activation
 - Prevent binding of gp120 or RANTES to CCR5 which induces apoptosis

Methods

Primary Objective/Endpoint

- To assess whether 24 weeks of MVC added to a subject's stable antiretroviral regimen is associated with \geq 20 cells/ μ L CD4+ T-cell count increase in subjects with suboptimal CD4+ T-cell response despite sustained virologic suppression
- Change in CD4 between baseline (pre-entry/entry average) to week 24 (week 22/24 average)

Study Population

- Age 16 or older
- CD4+ T-cell count <250/ μ L
- Plasma HIV-1 RNA below limit of detection for at least 48 weeks prior to entry
- Calculated CD4+ slope between -20 cells/ μ L/year and +20 cells/ μ L/year prior to entry

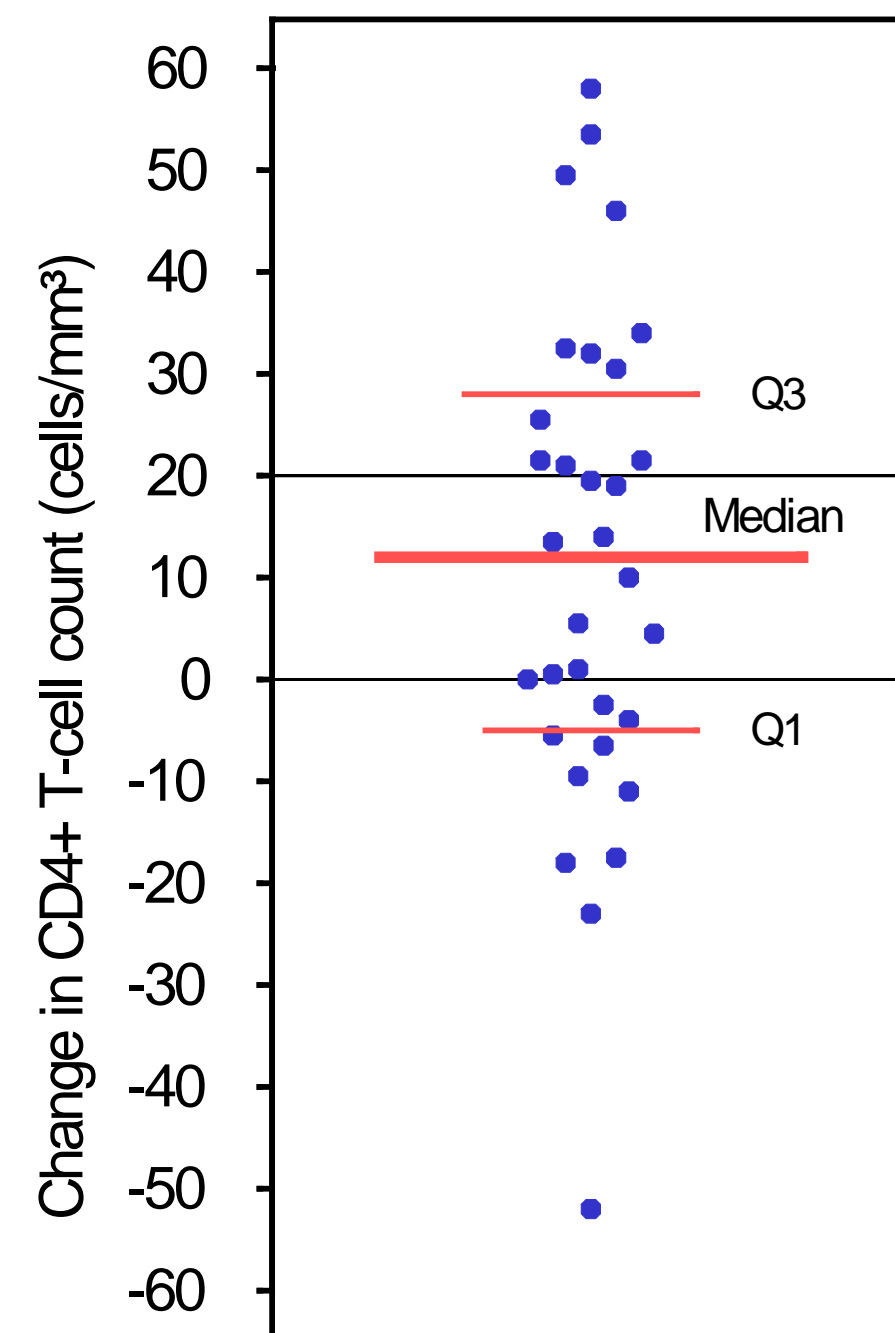
Intervention/Follow-up

- Subjects added MVC to their existing regimen at the standard dose for 24 weeks
- Followed for an additional 24 weeks off MVC (Data not yet available)
- CD4+ T-cell count at pre-entry, entry, 4, 8, 12, 16, 22, 24 weeks
- Advanced flow cytometry on fresh cells at pre-entry, entry, 12, 22 and 24 weeks

Table 1: Baseline characteristics

Characteristic	Total (N=34)
Age (years)	
Median [Q1, Q3]	50 [47, 55]
Min, Max	41, 64
Sex	
Male	32 (94%)
Female	2 (6%)
Race/ethnicity	
White Non-Hispanic	24 (71%)
Black Non-Hispanic	6 (18%)
Hispanic (Regardless of Race)	4 (12%)
Pre-entry nadir CD4 count (cells/mm³)	
\leq 50	23 (68%)
51 - 100	9 (26%)
101 - 200	2 (6%)
Pre-entry CD4 count slope/year	
Median [Q1, Q3]	5.81 [-14.02, 12.13]
Min, Max	-18.17, 18.05
Baseline CD4 count (cells/mm³)[†]	
Median [Q1, Q3]	153 [119, 203]
Min, Max	20, 272
Years with undetectable HIV-1 RNA prior to entry[‡]	
Median [Q1, Q3]	2.95 [1.80, 4.50]
Min, Max	1.00, 12.60

Figure 1: Distribution of change in CD4+ T-cell counts from baseline to week 22/24 (N=32)



Results

Figure 2: Median change in CD4+ T-cell count from baseline over time

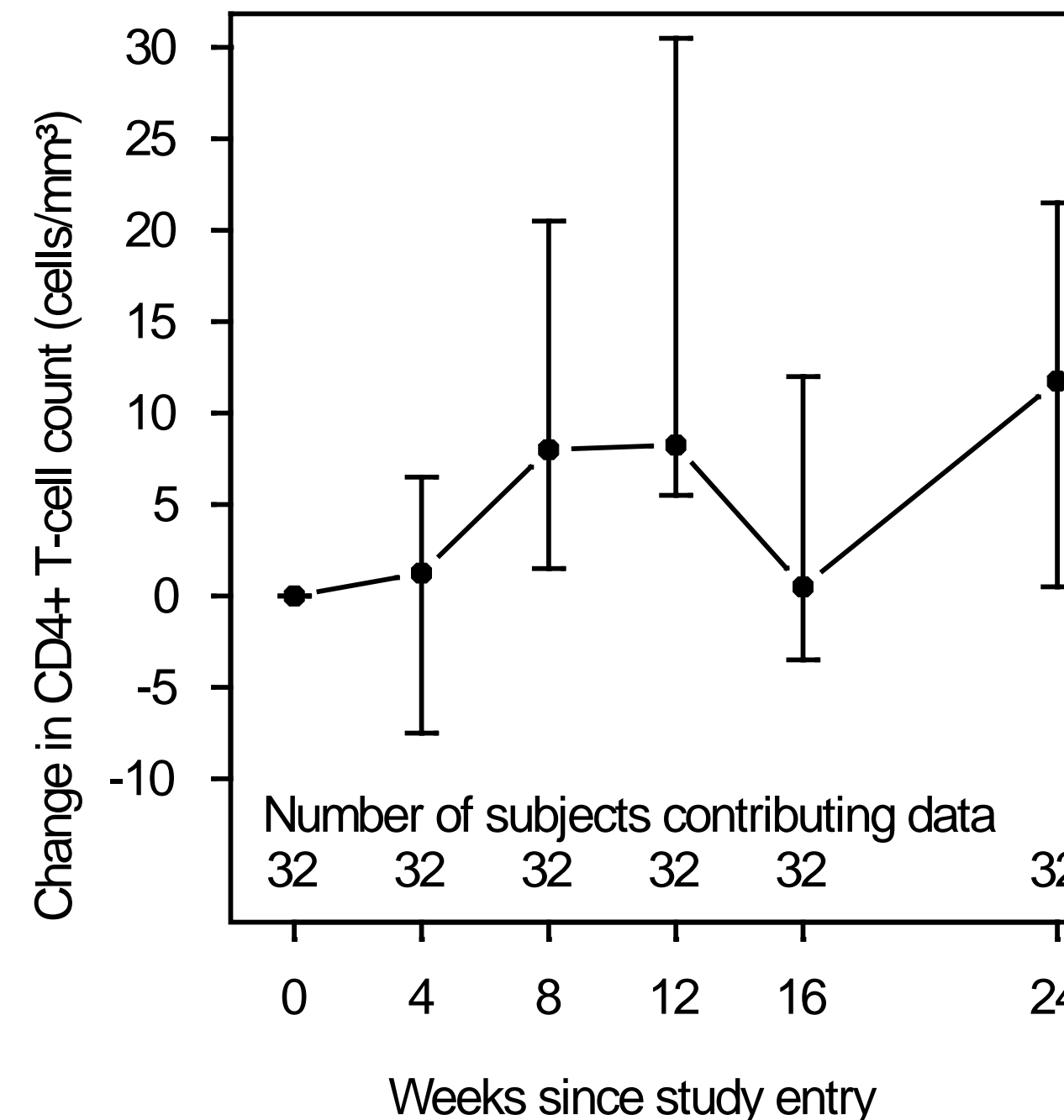


Figure 3: Pre and post MVC CD4+ T-cell count slopes

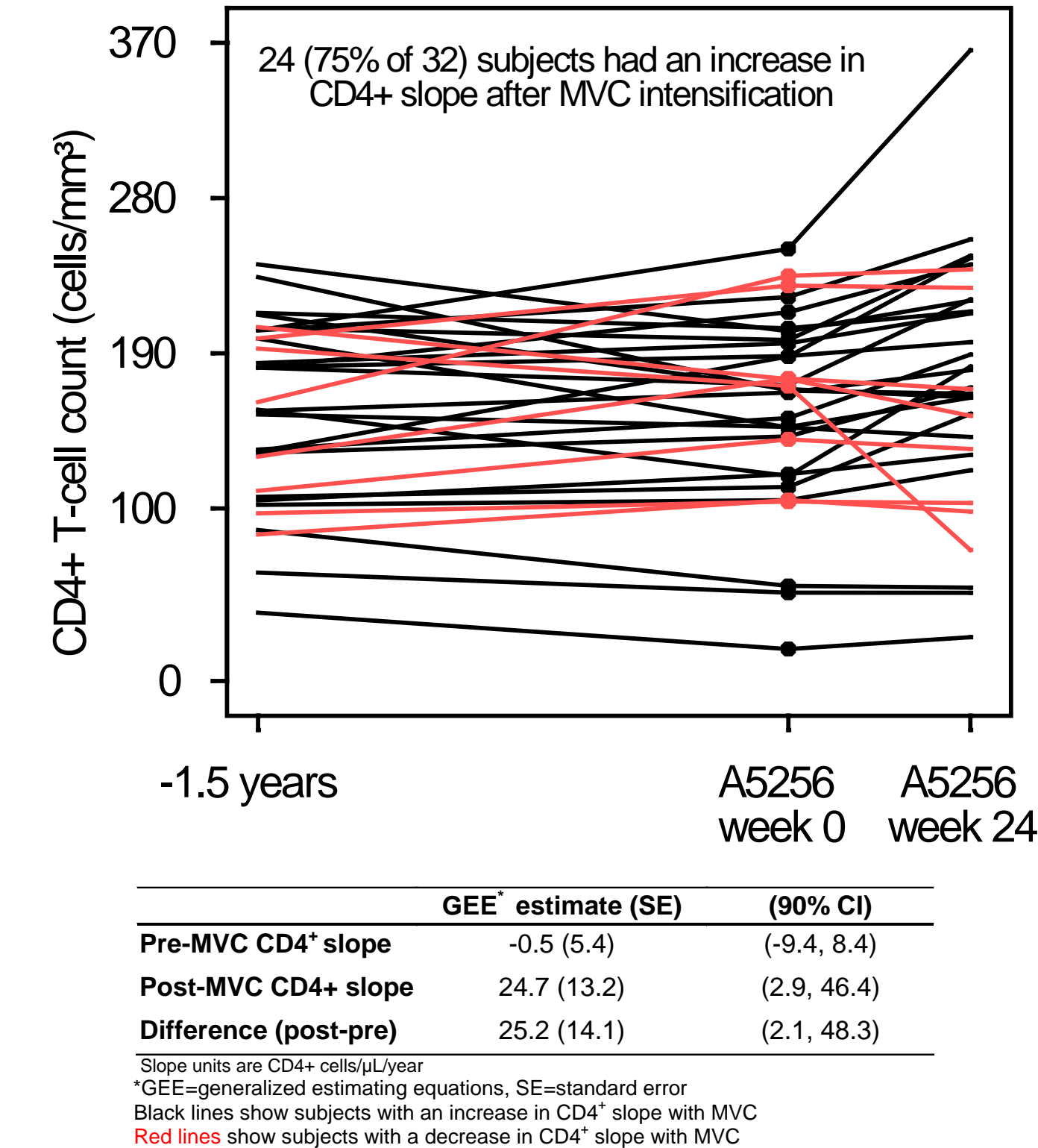


Table 2: Change to week 22/24 in T-cell Maturation Subsets, Immune Activation and Apoptosis

Immunologic marker	Baseline median (90% CI)	Change median (90% CI)	CD8+	
			Baseline median (90% CI)	Change median (90% CI)
T-Cell Subsets				
Central memory (%CD45RA ⁺ , CCR7 ⁺)	34.5 (32.3, 37.2)	-4.8 (-7.9, -1.9)	4.7 (3.9, 7.7)	-1 (-1.9, -0.5)
Naive (%CD45RA ⁺ , CCR7 ⁺)	19.3 (16.5, 23.7)	-1.3 (-3, 0.3)	20.6 (13.4, 25.7)	-3.3 (-5.4, -1.7)
Effector (%CD45RA ⁺ , CCR7 ⁺)	3.1 (2.6, 3.7)	0.7 (0, 0.9)	29.5 (26.2, 38.4)	2 (0.2, 6.6)
Effector memory (%CD45RA ⁺ , CCR7 ⁺)	43.1 (38.2, 47.5)	5.8 (2.5, 10.6)	37.9 (29.6, 42.3)	2.5 (0.8, 6)
Immune Activation				
%HLA-DR ⁺ , CD38 ⁺	5.3 (4.7, 6.3)	-1.3 (-1.8, -0.3)	8.7 (6.6, 11.8)	-1.4 (-3, -0.3)
%CD38 ⁺	45.2 (39.3, 51.8)	-14.8 (-19.6, -9.3)	29.6 (24.3, 43.6)	-14.2 (-19.5, -8.7)
%CD57 ⁺	6.5 (5.1, 10.1)	1.8 (1, 2.7)	35.3 (27.9, 46)	3.6 (1, 5.6)
%Ki67 ⁺	2.9 (2.5, 3.8)	-1 (-1.5, -0.5)	0.9 (0.8, 1.2)	-0.1 (-0.3, 0.1)
Apoptosis				
%caspase3 ⁺	1.7 (1.1, 2)	-1.1 (-1.4, -0.6)	1.1 (0.7, 1.4)	-0.7 (-0.9, -0.4)
%Bcl-2 ⁺	1.7 (1.2, 2.3)	0.7 (0, 1.3)	1.3 (0.8, 2.2)	0.5 (-0.1, 0.8)

- 2 subjects discontinued MVC for virologic failure and were excluded per protocol
- A CD4+ count increase of <20 cells/ μ L was not excluded for the primary endpoint (p=0.97; one-sided Wilcoxon signed-rank)
- The median increase in CD4+ T-cell count to week 22/24 was 12 cells/ μ L [90% CI 1, 22]
- Only 2 subjects had a CD4+ T-cell increase of \geq 50 cells/ μ L
- The decrease in %CD38⁺ or %CD38⁺/HLA-DR⁺ expression on CD4+ or CD8+ cells were not associated with CD4+ T-cell gain

Conclusions

- Adding MVC to a virologically suppressive antiretroviral regimen for 24 weeks was not associated with a clinically significant increase in CD4+ T-cell counts of at least 20 cells/ μ L.
- A small increase in CD4+ T-cell slope was observed (25 cells/ μ L/year), but not at the magnitude expected. This should be interpreted with caution in this single-arm pilot trial.
- Adding MVC was associated with decreased CD4+ and CD8+ activation as evidenced by reduced %CD38⁺, %HLA-DR⁺/CD38⁺, and improvement in markers of apoptosis. The clinical significance of these findings is unknown.
- Decreased activation did not correlate with CD4+ T-cell change suggesting that persistently low CD4+ T-cell counts in this population may not be related to ongoing immune activation.
- Further studies of CCR5 antagonists to dampen immune activation associated with complications of chronic HIV infection are warranted.

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